Medical Policy

Cytochrome p450 Genotyping

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Policy Number: 256
BCBSA Reference Number: 2.04.38
NCD/LCD: Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L35072)

Related Policies
- Genetic Testing for Mental Health Conditions, #669
- Genetic testing for Tamoxifen Treatment, #067
- Genetic testing for Warfarin Dose, #214
- Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines, #096

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

CYP450 genotyping for the purpose of aiding in the choice of clopidogrel versus alternative antiplatelet agents, or in decisions on the optimal dosing for clopidogrel, may be considered INVESTIGATIONAL.

CYP2D6 genotyping to determine drug metabolizer status may be considered MEDICALLY NECESSARY for patients:
- With Gaucher disease being considered for treatment with eliglustat; OR
- With Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day.

CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for the following drugs is considered INVESTIGATIONAL, aside from determinations in the separate policies noted above.
- Selection or dosing of selective serotonin reuptake inhibitors (SSRIs)
- Selection or dosing of selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
- Selection or dosing of tricyclic antidepressants
- Selection or dosing of antipsychotic drugs
- Selection or dosage of codeine
• Dosing of efavirenz and other antiretroviral therapies for HIV (human immunodeficiency virus) infection
• Dosing of immunosuppressant for organ transplantation
• Selection or dosing of beta blockers (e.g., metoprolol)
• Dosing and management of anti-tuberculosis medications.

The use of genetic testing panels that include multiple CYP450 mutations is considered INVESTIGATIONAL.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L35072)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information

Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required. Yes indicates that prior authorization is required. No indicates that prior authorization is not required. N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>No</th>
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<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
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<tr>
<td>Medicare HMO BlueSM</td>
<td>No</td>
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<tr>
<td>Medicare PPO BlueSM</td>
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</table>

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if medical necessity criteria are met:

<table>
<thead>
<tr>
<th>ICD-10-cm diagnosis codes:</th>
<th>code description</th>
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</thead>
<tbody>
<tr>
<td>E75.22</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td>G10</td>
<td>Huntington's disease</td>
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</table>

**Description**

**DRUG EFFICACY AND TOXICITY**

Drug efficacy and toxicity vary substantially across individuals. Because drugs and doses are typically adjusted, if needed, by trial and error, clinical consequences may include a prolonged time to optimal therapy. In some cases, serious adverse events may result.

Different factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation in genes coding for drug-metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

Pharmacogenomics is the study of how an individual's genetic inheritance affects the body's response to drugs. It may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA variants (genotyping) in genes related to the metabolic pathway (pharmacokinetics) or signal transduction pathway (pharmacodynamics) of the drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse effects, and decrease medical costs.

**CYTOCHROME P450 SYSTEM**

The cytochrome P450 (CYP450) family is a major subset of all drug-metabolizing enzymes; several CYP450 enzymes are involved in the metabolism of a significant proportion of currently administered drugs. CYP2D6 metabolizes approximately 25% of all clinically used medications (eg, dextromethorphan, β-blockers, antiarrhythmics, antidepressants, and morphine derivatives), including most prescribed drugs. CYP2C19 metabolizes several important types of drugs, including proton pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline.

Some CYP450 enzymes are highly polymorphic, resulting in some enzyme variants that have variable metabolic capacities among individuals, and some with little to no impact on activity. Thus, CYP450 enzymes constitute an important group of drug-gene interactions influencing the variability of effect of some CYP450-metabolized drugs.

Individuals with 2 copies (alleles) of the most common (wild-type) DNA sequence of a particular CYP450 enzyme gene resulting in an active molecule are termed extensive metabolizers (normal). Poor metabolizers (PMs) lack active enzyme gene alleles, and intermediate metabolizers, who have 1 active and 1 inactive enzyme gene allele, may experience to a lesser degree some of the consequences of PMs. Ultrarapid metabolizers (UMs) are individuals with more than 2 alleles of an active enzyme gene. There is pronounced ethnic variability in the population distribution of metabolizer types for a given CYP enzyme.
UMs administered an active drug may not reach therapeutic concentrations at usual recommended doses of active drugs, while PMs may suffer more adverse events at usual doses due to reduced metabolism and increased concentrations. Conversely, for administered prodrugs that must be converted by CYP450 enzymes into active metabolites, UMs may suffer adverse events and PMs may not respond.

Many drugs are metabolized to varying degrees by more than 1 enzyme, either within or outside of the CYP450 superfamily. In addition, interaction between different metabolizing genes, interaction between genes and environment, and interactions among different nongenetic factors also influence CYP450-specific metabolizing functions. Thus, identification of a variant in a single gene in the metabolic pathway may be insufficient in all but a small proportion of drugs to explain interindividual differences in metabolism and consequent efficacy or toxicity.

**DETERMINING GENETIC VARIABILITY IN DRUG RESPONSE**

Genetically determined variability in drug response has been traditionally addressed using a trial-and-error approach to prescribing and dosing, along with therapeutic drug monitoring (TDM) for drugs with a very narrow therapeutic range and/or potential serious adverse events outside that range. However, TDM is not available for all drugs of interest, and a cautious trial-and-error approach can lengthen the time to achieving an effective dose.

CYP450 enzyme phenotyping (identifying metabolizer status) can be accomplished by administering a test enzyme substrate to a patient and monitoring parent substrate and metabolite concentrations over time (eg, in urine). However, testing and interpretation are time-consuming and inconvenient; as a result, phenotyping is seldom performed.

The clinical utility of CYP450 genotyping (ie, the likelihood that genotyping will significantly improve drug choice, dosing, and patient outcomes) is favored when the drug under consideration has a narrow therapeutic dose range, when the consequences of treatment failure are severe, and/or when serious adverse reactions are more likely in patients with gene sequence variants. Under these circumstances, genotyping may direct early selection of the most effective drug or dose, and/or avoid drugs or doses likely to cause toxicity. For example, warfarin, some neuroleptics, and tricyclic antidepressants have narrow therapeutic windows and can cause serious adverse events when concentrations exceed certain limits, resulting in cautious dosing protocols. Yet, the potential severity of the disease condition may call for immediate and sufficient therapy; genotyping might speed up the process of achieving a therapeutic dose and avoiding significant adverse events.

**Summary**

The cytochrome P450 (CYP450) family is involved in the metabolism of many currently administered drugs, and genetic variants in cytochrome P450 are associated with altered metabolism of many drugs. Genetic testing for cytochrome P450 variants may assist in selecting and dosing drugs that are affected by these genetic variants.

For individuals with need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy managed with testing for CYP2C19 metabolizer status by CYP2C19 genotyping, the evidence includes multiple systematic reviews, secondary analyses of a RCT and multiple observational studies. Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity and mortality. Multiple observational studies report that genetic variants associated with CYP2C19 may be associated with a modest increase in the rate of stent thrombosis and increased incidence of adverse clinical events. However, 2 large meta-analysis that included patients treated with and without percutaneous coronary intervention showed conflicting results of the impact of CYP2C19 variants on clinical outcomes. The evidence addressing whether the use of CYP2C19 genotype-directed therapy improves clinically meaningful outcomes is limited. RCTs have shown that rapid genotyping with subsequent personalized treatment reduces the number of carriers treated who exhibit high on-treatment platelet reactivity compared to those managed without genetic testing. A prospective cohort study reported that in patients with a recent acute coronary syndrome or percutaneous coronary intervention who underwent CYP2C19 genotyping, providers were more likely to increase antiplatelet therapy.
intensification for carriers than for noncarriers. A randomized, prospective study comparing the clinical utility of genetic testing versus standard clinical management is required to better understand the relative merit of management options. Given the association between CYP2C19 metabolizer status and risk of stent thrombosis in patients undergoing cardiac interventions, genotype may be used to consider treatment alternatives (eg, higher doses of clopidogrel or alternative drug choices). The U.S. Food and Drug Administration (FDA) created a black box warning indicating testing should be considered. Clinical input from academic medical centers and specialty societies was mixed concerning the benefit of genetic testing, but there was not consensus that the medically necessary determination be changed. However, since clinical input was obtained and the black box labeling was created, additional evidence has accumulated that CYP2C19 genotype is not associated with differences in the magnitude of benefit for patients treated with clopidogrel. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with Gaucher disease type 1 who are undergoing or being considered for treatment with eliglustat who are managed with testing for CYP2D6 metabolizer status by CYP2D6 genotyping, the evidence consist of subgroup analysis of clinical trial data submitted to FDA by the manufacturer as part of regulatory submission. Relevant outcomes are test accuracy and validity, morbid events, medication use, and treatment-related morbidity. Eliglustat tartrate is primarily metabolized by CYP2D6. FDA review report that at doses as high of 200 mg twice daily the exposure in UMs was about 57% and about 82% lower than the exposures for EMs and IMs at 100 mg twice daily, respectively. Based on this high variation in drug exposure based on metabolizer status, the FDA label requirement for genotyping of CYP2D6 to determine metabolizer status before the use of eliglustat may be clinically reasonable and UMs be excluded from being prescribed eliglustat because these patients may not achieve adequate concentrations to achieve a therapeutic effect. Although there is no published evidence about outcome changes associated with genotype-directed therapy for this medication, there are changes in management that are likely to occur with differences in genotypes. The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals with Huntington disease who are undergoing or being considered for treatment with tetrabenazine who are managed with testing for CYP2C19 metabolizer status by CYP2C19 genotyping, the evidence consists of a single cohort study. Relevant outcomes are test accuracy and validity, morbid events, medication use, and treatment-related morbidity. The FDA labeling for the orphan drugs tetrabenazine for Huntington disease recommends CYP2D6 genotyping before use. There is limited published evidence about outcome changes associated with genotype-directed therapy for this medication. One cohort study report that patients categorized as UMs by a CYP450 genotype test require high dose of tetrabenazine compared to those who are not categorized as UMs. However, this finding was based in a sample of 127 patients of whom only 2 were categorized as UMs. Therefore, these findings have to be reproduced in a larger cohort. The evidence is insufficient to determine the effects of the technology on health outcomes.

Although the evidence is limited for the use of CYP2C19 genotyping in patients undergoing or being considered for treatment with tetrabenazine, given the FDA labeling and the potential for high variation in drug exposure based on metabolizer status, genotyping of CYP2D6 to determine metabolizer status before use of tetrabenazine may be clinically reasonable. CYP2C19 may be considered medically necessary in patients with Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day.

For individuals who are undergoing or being considered for treatment with selective serotonin reuptake inhibitors who are managed by CYP450 genotyping, the evidence includes 1 systematic review and multiple retrospective and prospective studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Multiple retrospective and prospective studies have evaluated the association between selective serotonin reuptake inhibitors (SSRIs) and CYP450 variants and reported conflicting results. Based on a systematic review of the evidence, Evaluation of Genomic Applications in Practice and Prevention (EGAPP) group concluded that there was insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for nonpsychotic depression. At
present, the clinical utility of CYP450 testing is also poorly defined. It is not known if CYP450 genotype-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate, compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with selective serotonin-norepinephrine reuptake inhibitors who are managed by CYP450 genotyping, the evidence includes post hoc reanalysis of several RCTs. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbidity, events, medication use, and treatment-related morbidity. Post hoc reanalysis of data from multiple RCTs has correlated treatment response to venlafaxine with genetic status. However, the clinical utility of CYP450 testing is poorly defined. It is not known if CYP450 genotype-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with tricyclic antidepressants who are managed by CYP450 genotyping, the evidence includes multiple observational studies. Relevant outcomes are test accuracy, test validity, symptoms, change in disease status, morbidity, events, medication use, and treatment-related morbidity. These studies have shown that poor metabolizers have high serum concentrations of tricyclic antidepressants drugs and extensive metabolizers have low serum concentrations. However, the observed differences were unlikely to have clinically important effects. At present, the clinical utility of CYP450 testing is also poorly defined. It is not known if CYP450 genotyping guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with antipsychotic drugs who are managed by CYP450 genotyping, the evidence includes 1 systematic review and multiple observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbidity, events, medication use, and treatment-related morbidity. Observational studies have suggested that individuals with genetic variants in the CYP450 gene may be at increased risk for adverse effects of antipsychotic drugs, particularly extrapyramidal effects such as tardive dyskinesia. However, a large systematic review and meta-analyses of 47 studies found no convincing evidence of an association between test results and either drug efficacy or toxicity. When seen, adverse effect differences (an association, eg, with tardive dyskinesia) were considered too small to be clinically meaningful. At present, the clinical utility of CYP2D6 testing is also poorly defined. It is not known if CYP450 genotype-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with codeine who are managed by CYP450 genotyping, the evidence includes few case reports. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbidity, events, medication use, and treatment-related morbidity and mortality. Enhanced CYP2D6 activity is associated with risk of accelerated codeine metabolism to high levels of circulating morphine in rapid metabolizers, which is thought to have contributed to deaths in infants of nursing mothers prescribed codeine and in pediatric patients post tonsillectomy. In addition, the American Academy of Pediatrics recommends that codeine should not be used in children under 12 at all. There is limited evidence about the clinical validity of testing for CYP450 genotype. At present, the clinical utility of CYP2D6 testing is also poorly defined. It is not known if CYP450 genotyping guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with highly active antiretroviral agents who are managed by CYP450 genotyping, the evidence includes multiple observational studies.
Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Multiple small and large observational studies have shown association between variants in CYP450 and higher drug levels, CNS adverse effects and treatment discontinuation. At present, the clinical utility of CYP450 testing is also poorly defined. It is not known if CYP450 genotyping guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with immunosuppressant therapy for organ transplantation who are managed by CYP450 genotyping, the evidence includes multiple systematic reviews and multiple observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity and mortality. Multiple observational studies including a large systematic review showed that individuals who express CYP3A5 (extensive and intermediate metabolizers) generally have decreased dose-adjusted trough concentrations of tacrolimus as compared with those who are CYP3A5 nonexpressers (poor metabolizers), possibly delaying achievement of target blood concentrations. The evidence addressing whether the use of CYP450 genotype-directed therapy improves clinically meaningful outcomes is limited. One RCT demonstrated that the use of a CYP450 genotype-directed algorithm was associated with improvements in the proportion of patients with target tacrolimus concentration ranges; no differences in morbidity or mortality or graft survival were reported. Additional studies of the clinical utility of CYP450 genetic testing-based algorithms in tacrolimus management are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

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<th>Date</th>
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<tbody>
<tr>
<td>8/2017</td>
<td>BCBSA National medical policy review. New references added. Background and summary updated. 8/2017</td>
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<tr>
<td>5/2016</td>
<td>BCBSA National medical policy review. Medically necessary statements for CYP2B6 genotyping for patients being considered for eliglustat or tetrabenazine therapy added; “for all drugs” statement removed from investigational statement; medical necessary statement for CYP2C19 genotyping for patients receiving clopidogrel therapy changed to investigational. Effective 5/1/2016.</td>
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<tr>
<td>7/2015</td>
<td>Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L34499) added.</td>
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<tr>
<td>1/2014</td>
<td>New references added from BCBSA National medical policy.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**


57. de Leon J. The crucial role of the therapeutic window in understanding the clinical relevance of the poor versus the ultrarapid metabolizer phenotypes in subjects taking drugs metabolized by CYP2D6 or CYP2C19. J Clin Psychopharmacol. Jun 2007;27(3):241-245. PMID 17502769


64. Macaluso M, Preskorn SH. CYP 2D6 PM status and antidepressant response to nortriptyline and venlafaxine: is it more than just drug metabolism? J Clin Psychopharmacol. Apr 2011;31(2):143-145. PMID 21346604


85. King J, Aberg JA. Clinical impact of patient population differences and genomic variation in efavirenz therapy. AIDS. Sep 12 2008;22(14):1709-1717. PMID 18753940


